NT-4, brain-derived neurotrophic factor, leukemia inhibitory factor, tenascin-C, ninjurin, neural cell adhesion molecule, and neural agrin, wherein neural sprouting in said treated tissue is inhibited, and

b) contacting said tissue with a clostridial neurotoxin.

REMARKS

The Examiner has rejected pending claims 1-6, 9 and 16 as allegedly failing to meet the written description requirement of 35 USC §112(1). Applicants respectfully traverse this rejection.

The Examiner has cited the PTO Interim Guidelines on Written Description, 64 Fed. Reg. 71427 (1999) as support for this rejection. The PTO Final Guidelines on Written Description Requirement, 66 Fed. Reg. 1099 (Jan. 2001) (the "Guidelines") supercede the interim guidelines, although neither has the force of law. The Guidelines make clear that "[t]here is a strong presumption that an a adequate written description of the claimed invention is present when the application is filed." *Id.* at 1105. Such a presumption is present if the invention is either adequately described in the specification or is known to one of ordinary skill in the art. See *id.*

Claim 1 of the present claims has been subject to one amendment, a functional clause specifying that the method results in the inhibition of neural sprouting. However, the Examiner's rejection is not that the inhibition of neural sprouting is not adequately described, but rather that CNTF-inhibiting moieties are not adequately described; thus for all intents and purposes the Examiner is rejecting original claims. As such, the Examiner must overcome the strong presumption by clear and convincing evidence, thereby establishing a *prima facie* case that these claims violate the written description requirement. Applicants respectfully submit that the Examiner has not done this.

The Examiner states that the specification does not describe any inhibitory agent capable of inhibiting expression of CNTF. This is not accurate. The specification incorporates by reference detailed descriptions, including nucleotide sequence information, of ribozyme catalytic sites, cleavage sites, and other characteristics. See e.g., Usman et al., 10 Nucleic Acids and Mol. Biol. 243 (1996), incorporated by reference as part of this specification. Thus, Figure 2 of Usman provides the sequence requirements for a hammerhead ribozyme; Figure 4 of this reference provides the relevant structural features of a nuclease stable hammerhead ribozymes, etc. Moreover, the nucleotide sequence CNTF cDNA (and the ribozyme substrate mRNA), was well known to those of skill in the art (See Lam, et al., *Gene* 102 (2), 271-276 (1991)) and publicly available through GenBank at http://www.ncbi.nlm.nih.gov/ at the time the application was filed. That which is well known to the person of ordinary skill in the art such that he can reasonably conclude the inventor had possession of the invention at the time of filing need not be described; Applicants respectfully believe they have met this burden.

The Court of Appeals for the Federal Circuit has recently made clear that "a description of a genus of cDNAs may be achieved by . . . recitation of structural features common to members of the genus . . . ", *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). With the adequate disclosure of the

CNTF substrate sequence and catalytic ribonucleotide structural and sequence requirements, Applicants submit this is exactly what has been done in the present case.

However, this is largely beside the point. Applicant notes that a genus of ribozymes or antisense agents is not what is being currently claimed. Rather, the invention is directed to a method of extending the effective period during which tissue treated with a clostridial toxin is paralyzed, wherein such result is achieved by inhibition of expression of CNTF. Applicant submits that, for example, Example 3 and International Patent Publication WO95/32738 (also incorporated by reference) adequately describes an exemplary delivery system for ribozymes or antisense agents.

For these reasons, Applicants respectfully submit that the Examiner has not met the high burden of establishing a *prima facie* case that the Applicants have not met the written description requirement, and thus request this rejection be reconsidered and withdrawn.

Enablement

The Examiner has also rejected the present claims as allegedly not being enabled by the specification. Applicants respectfully traverse this rejection.

The Examiner appears to argue that the claimed methods, drawn to administering an agent which inhibits expression of CNTF, are not enabled because 1) the *in vivo* use of antisense and ribozyme agents are allegedly unpredictable, 2) no specific molecules are disclosed, and 3) the specification allegedly does not teach how to use such an agent. Applicants will a address these grounds one at a time.

With regard to the first ground of rejection, Applicants note that the Examiner cites Dietz and Baier for the proposition that suppression of gene expression with a given agent (such as an antisense or ribozyme agent) does not always result in a decrease in biological activity. Before reaching the merits of the argument, Applicants respectfully suggest that if this is the ground of rejection, then the Examiner appears to doubt the utility of the claimed invention as a whole, and might better present the rejection as a utility rejection.

The invention is drawn to a method of inhibiting CNTF expression wherein neural sprouting is inhibited. Thus, methods of inhibiting CNTF expression which do not result in an inhibition of biological effect are not claimed. Merely because the Examiner can find examples of cases in which inhibition of expression does not lead to a reduction in a biological activity does not mean that the present invention is not enabled. Applicant has provided an example how to introduce a ribozyme or antisense agent into a cell; i.e., by a clostridial neurotoxin-based delivery system. This delivery system is highly specific for target neurons by virtue of the receptor binding moiety present in the heavy chain of the neurotoxin. The active agent is actively transported within the target neuron by the same mechanism that results in botulinum or tetenus toxicity. Details on the construction of such agents is provided in International Patent Publication WO95/32738, incorporated by reference as part of this specification.

Regarding the alleged lack of disclosure of how to make antisense or ribozyme agents for targeting CNTF

DNA or mRNA in the claimed methods, reference is made to the discussion above. Additionally, as affirmed consistently by the Court of Appeals for the Federal Circuit, the specification "need not teach, and preferably omits, what is well-known in the art." *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987) (quoting *Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Recently, the Court of Appeals for the Federal Circuit has again made clear that the person of ordinary skill in the biochemical arts must be considered to possess considerable skill. *Johns Hopkins University v. Cellpro, Inc.*, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998) (holding that deposit of a single hybridoma cell line containing a single monoclonal antibody provided sufficient teaching to enable one to make and use the genus of monoclonal antibodies specifically binding to the same antigen without undue experimentation.) Required design features for effective antisense and ribozyme agents (such as the use of nuclease-resistant modified nucleotides, etc.) are provided in the references cited on page 9 of the specification; additionally the person of skill in the art is charged with knowledge of all prior art; thus such a person would be aware of the pitfalls mentioned in papers such as Goode, cited by the Examiner, and could effective design around them. Merely because experimentation resulting in some failures may be required to make or use a claimed invention does not obviate enablement.

Thus, the specification provides ample examples of how to make the agents to be used in the claimed methods.

Finally, the Examiner claims that the specification does not teach the person of skill in the art how to use the invention. But the specification clearly gives an example in which a ribozyme -- although an anti-agrin ribozyme is mentioned, the delivery method encompasses any ribozyme regardless of the specific molecular target within the neural cell -- is introduced specifically within a neural cell using a modified neurotoxin. Other methods of introducing oligonucleotides or ribozymes into cells (e.g., microinjection and liposome delivery) are well-known in the art. Moreover, speculation that certain such methods may be less efficacious than others is irrelevant to enablement of the invention. Applicants make no claim that one delivery system is better than another, only that inhibition of neural sprouting by inhibiting expression of CTNF will result in a longer effective period for treatment of a patient with a therapeutic neurotoxin.

To this last point, the Examiner has commented that one or more dependent claim is drawn to administering a neurotoxin after administering the inhibitory agent, and wonders how this can be, since the exemplary method requires the ribozyme to be conjugated to a modified neurotoxin. Applicants regret any confusion experienced by the Examiner in this respect; as indicated in International Patent Publication WO95/32738, the modified neurotoxin carrier often does not contain an active endoprotease moiety; thus, according to the claim the subject is treated with the delivery device, then with an active neurotoxin having a catalytically active endoprotease.

For the above reasons, Applicants request that this ground of rejection be withdrawn.

Indefiniteness

The Examiner has rejected all claims as allegedly indefinite for omitting essential steps, because the specification is said not to teach that neural sprouting can be inhibited without treatment with a clostridial toxin. Claim 1 has now been accordingly amended to add a step wherein the tissue is treated with a neurotoxin.

The claims were held to be allegedly indefinite in being drawn partially to non-elected subject matter. Accordingly, Claim 1 has been amended to state that the method comprises preventing the expression of the target protein.

The claims were held allegedly indefinite for reciting "neural sprouting"; ther Examiner expressed confusion whether initial sprouting or continued growth of the sprouts was meant by this phrase. As indicated in the specification, "one may therapeutically intervene at one of the major steps of the sprouting phenomenon to prevent or attenuate the neural sprouting . . . ." Specification at sentence bridging pages 14 and 15. Thus, either the initial appearance or continued growth of neural sprouts is intended by the phrase, and this is submitted to be clear from the specification.

For the above reasons, Applicants request that the Examiner withdrawn the indefiniteness rejection.

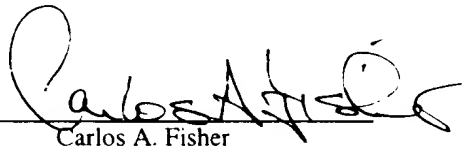
Applicants would also point out that the amendments made herein were made only with regard to the elected invention, and were caused by the restriction requirement and election of species requirement. Thus, no narrowing amendment was made for reasons related to patentability.

CONCLUSION

For the reasons indicated above, Applicants respectfully urge the Examiner to reconsider and withdraw the standing rejections. While no fee is thought to be required with regard to this communication, if Applicants are in error please use our Deposit Account 01-0885 for the payment of any fees that may be due.

Respectfully Submitted,

Date: 10/19/01

Signature: 

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MARKED-UP VERSION OF AMENDED CLAIM

1. (Twice Amended) A method for extending the effective period during which tissue treated with a clostridial toxin is paralyzed comprising:

   a) contacting said tissue with a composition comprising an agent able to prevent the expression [neuroregenerative activity] of a polypeptide selected from the group consisting of: IGF I, IGF II, cilary neurotrophic factor, NT-3, NT-4, brain-derived neurotrophic factor, leukemia inhibitory factor, tenascin-C, ninjurin, neural cell adhesion molecule, and neural agrin, wherein neural sprouting in said treated tissue is inhibited, and

   b) contacting said tissue with a clostridial neurotoxin.